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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,294	NIELSEN ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10-22,25-40 and 78-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,10-22,25-40 and 78-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of December 5, 2005 on April 7, 2006. Claims 1, 78-80 are amended. Claims 2, 6-9, 23, 24, 41-77 are cancelled.

Claims 1, 3-5, 10-22, 25-40, 78-80 are under consideration. It is noted, per the Restriction Requirement, February 1, 2005, that the invention is drawn to nucleic acids that encode p53. While claims 1 and 80 are limited to nucleic acid p53 delivery, claim 79 still recites non-elected subject matter.

It is noted that Applicant has amended claim 80 and has not used the appropriate status identifier of the amended claim, per guidelines of the MPEP, see MPEP 714, II.C. (C) and CFR 1.121. The amendment is not in compliance with 37 CFR 1.121 (c) and while it has been entered, future amendments must comply or risk not being entered. Claim 80 has been interpreted as "amended" in this Office Action.

Information Disclosure Statement

Applicant filed an Information Disclosure Statement (IDS) on April 7, 2006. The IDS has been considered.

Withdrawn Rejections

35 U.S.C. § 102/103

Applicant's arguments, see page 9 of Applicant's response, filed April 7, 2006, with respect to the rejection of claims 1, 3, 4, 5, 9, 10, 18-22, 25, 26, 28, 31-33, 37, 38, 78-80 as being anticipated, or in the alternative, obvious over U.S. Patent No. 5,747,469

to Roth, et al. have been fully considered and are persuasive. Applicant has indicated that Roth et al. do not teach taxane. Further, Roth et al. do not teach that DNA damaging factors (e.g. cisplatin) are the same as agents such as taxane (Applicant's response, page 9). The rejection of claims 1, 3, 4, 5, 10, 18-22, 25, 26, 28, 31-33, 37, 38, 78-80 has been withdrawn. It is noted that the rejection of claim 9 is withdrawn as claim 9 is cancelled.

35 U.S.C § 103

Applicant's arguments, see page 11, filed April 7, 2006, with respect to the rejection of claims 1, 4, 5 as obvious over Roth et al. have been fully considered and are persuasive. Roth et al. do not teach any taxane. The rejection of claims 1, 4, 5 has been withdrawn.

Applicant's arguments, see page 11, filed April 7, 2006, with respect to the rejection of claims 1 and 9 as obvious over Roth et al. in view of Verma and Somia have been fully considered and are persuasive. Roth et al. do not teach any taxane. The rejection of claim 1 has been withdrawn. It is noted that the rejection of claim 9 is withdrawn as claim 9 is cancelled.

Applicant's arguments, see page 11, filed April 7, 2006, with respect to the rejection of claims 1, 3, 4, 5, 9-12, 15-22, 25, 26, 28, 31-33, 37, 38, 78-80 as obvious over Roth et al. in view of Moojoo et al. have been fully considered and are persuasive. Roth et al. do not teach any taxane. The rejection of claims 1, 3, 4, 5, 9-12, 15-22, 25,

26, 28, 31-33, 37, 38, 78-80 has been withdrawn. It is noted that the rejection of claim 9 is withdrawn as claim 9 is cancelled.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 10-22, 25-40, 78-80 remain rejected in modified form under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) an *in vivo* method for reducing the size of a tumor in a mammal comprising mammalian cancer cells deficient in functional p53, said method comprising directly contacting cancer cells with an adenoviral vector comprising a nucleic acid encoding p53, and also contacting said cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that growth of said cancer cells is reduced and/or said cancer cells undergo apoptosis, and

2) an *in vivo* method of treating mammalian cancer cells deficient in functional p53, wherein said method comprises administering directly at cancer cells, a DNA vector comprising a nucleic acid encoding p53, and contacting cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that growth of said cancer cells is reduced or such that said cancer cell undergo apoptosis,

does not reasonably provide enablement for

1) an *in vivo* method of treating mammalian cancer cells deficient in functional p53, wherein said method comprises contacting cancer cells with any DNA vector comprising a nucleic acid encoding p53, wherein said vector is administered by any route, and contacting said cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that one or more disease characteristic of the cells is ameliorated, wherein the mammalian cancer cells are human head and neck, ovarian, prostate, or mammary cancer cells, and

2) an *in vivo* method of treating any human head and neck, ovarian, prostate, or mammary cancer cells, including those not deficient in p53, wherein said method comprises contacting cancer cells with any vector comprising a nucleic acid sequence encoding p53, and contacting cells with a microtubule affecting agent, wherein the microtubule affecting agent comprises a taxane, such that one disease characteristic of the cancer cell is ameliorated.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record, December 5, 2005.

Response to Arguments

Applicant's arguments filed April 5, 2006 have been fully considered but they are not persuasive.

While Applicant has amended the claims 1, 78-80 to address the issues of enablement, the claim amendments do not address all issues discussed on pages 7-12 of the Office Action.

With regard to the scope of treating any disease characteristic of cancer cells, while the art and specification teaches reduction of tumor size, the specification and the art teach that treatment of metastatic cancer is not routine in the art (see, for example, claim 80). As such, the issue regarding this issue of enablement remains.

With regard to the issue of delivery of the adenoviral vector and plasmid comprising the nucleic acid encoding p53, the Office Action, pages 9-10, discussed the problems in the art with regard to systemic administration of vector and plasmid. While the discussion of systemic administration focused on the problems of biodistribution as it applied to proteins, the same discussion is applied to nucleic acids: there is exclusive clearance of the administered protein/nucleic acids by the liver. In addition to this, the art teaches that there is unpredictability in administering a nucleic acid vector across various species of animals, see Goinin and Galliard, 2004. As such, the issues regarding this issue of enablement remains. It is noted that claim 33 is drawn to many different routes of delivery. Because claims 1 and 80 (and subsequently claims 3-5, 10-22, 25-40) are not so limited as to route of delivery, they are included in the rejection.

For these reasons, the rejection to the claims remains.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-22, 25-27-30, 35, 37 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 depends on claim 29. Claim 29 has the limitation of contacting the tumor cell via intra-arterial injection and claim 30 has the same limitation of contacting the tumor, although the contacting is via intraperitoneal administration. It is unclear how intra-arterial is the same as intraperitoneal.

Claims 20-22, 25-27-30, 35, 37 depend on claim 1. Claims 20-22, 25-27-30, 35, 37 are drawn to proteins. However, there is no antecedent basis for "protein" in claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 10, 18-22, 25-28, 31, 78, 79, 80 are newly rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious, over Tocque, U.S. Patent 6,262,032, patented July 17, 2001, see IDS.

Tocque teaches a method of destroying a hyperproliferative cell in a tumor of an animal comprising administering a transgene construct comprising a nucleic acid sequence encoding p53 and a chemotherapeutic agent. Tocque teach H460 cells were transfected *in vitro* with a cDNA coding for the wild-type p53 protein placed in a plasmid under the control of a CMV promoter and were further treated with taxotere (Tocque, Example 3). Tocque teaches that the treatment with the p53 vector and taxotere reduce the number of H460 colonies more than by a treatment with taxotere only (Tocque, Fig. 3B). While Tocque teach one type of cells, Tocque contemplates that that the method is applied to cancer cells from a variety of tissues, including colon, thyroid, and myeloid leukaemias (Tocque, col. 4, 6th parag.). Tocque teaches that the vector comprising a nucleic acid sequence encoding p53 and a taxane can be administered *in vivo* by intratumoral injection and that in order to obtain a maximum expression in a maximum number of dividing cells, administration of the transgene is repeated (Tocque, col. 13, parag. under "Administration Protocol", see also claims). In addition to plasmid, Tocque teaches the use of adenoviral vector (Tocque, col. 10, lines, 41-42, also see claims).

Tocque teaches that the nucleic acid vector is in an injectable form and thus is in a vehicle which is pharmaceutically acceptable for injection (Tocque, col. 4, 1st parag.). Tocque teaches that the two agents (nucleic acid vector and chemotherapeutic agent) may be used simultaneously, separately, or spread over time (Tocque, col. 4, 3rd parag.).

Thus, Tocque anticipate claims 1, 3, 10, 18-22, 25-28, 31, 78, 79, 80.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 10-13, 15-22, 25-28, 31, 34, 78-80 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque, U.S. Patent 6,262,032, patented July 17, 2001, see IDS, in view of Gregory et al. U.S. Patent 5,932,210, patented August 3, 1999.

As described above in the 102 rejection, Tocque teaches a method of destroying hyperproliferative cells comprising a transgene construct comprising a nucleic acid sequence encoding wild-type p53 and a taxane.

While Tocque teaches these embodiments, Tocque does not teach a method using the an adenoviral vector comprising modifications as described in claims 11-17 or an A/C/N/53 or A/M/N/53 adenoviral vector.

Gregory et al. teach the A/C/N/53 and A/M/N/53 vectors. Gregory et al. teach that to reduce the frequency of contamination with wild-type adenovirus, it is desirable to improve either the virus or the cell line to reduce the probability of recombination. This can be achieved by increasing the size of the deletion in the recombinant virus and thus reduce the extent of shared sequence between it and the Ad5 in the 293 cells (Gregory et al., col. 5, 1st parag. under "Detailed Description of the Invention"). Gregory et al. provide the steps used to arrive at the A/C/N/53 and A/M/N/53 constructs (Gregory

et al., col. 3, lines 54-65, col. 16, lines 28-53, also Fig. 4) and indicate that the p53 recombinants are based on Ad5 and have had the E1 region of nucleotides 360-3325 replaced with a 1.4 kb full length p53 cDNA driven by the Ad 2 MLP (A/M/53) or human CMV (A/C/53) promoters followed by the Ad 2 tripartite leader cDNA. The remaining E1b sequence (705) nucleotides have been deleted to create the protein IX deleted constructs A/M/N/53 and A/C/N/53. The constructs also have a 1.9 kb Xba I deletion within adenovirus type 5 region E3.

Gregory et al. teach that A/M/N/53 was administered peritumorally twice a week for a total of 8 doses into nude mice injected 2 weeks prior with H69 cells (SCLC, p53 null). Gregory et al. teach that tumors treated with buffer or adenovirus that did not contain the nucleic acid sequence encoding p53 grew rapidly, while mice treated with A/M/N/53 had tumors that grew at a greatly reduced rate (Gregory et al., col. 20, lines 28-37, see also Fig. 7A).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral constructs, A/C/N/53 or A/M/N/53 in a method of destroying a hyperproliferative cell.

One having ordinary skill in the art would have been motivated to use the A/C/N/53 or the A/M/N/53 adenoviral vectors of Gregory et al. in the method of destroying hyperproliferative cells in the method taught by Tocque. Motivation for using the adenoviral vectors was provided by the fact that Gregory et al. teach that the vectors were made to reduce the probability of recombination between virus and cell line and by the fact that Gregory et al. teach that A/M/N/53 reduced tumor growth in nude mice.

There would have been a reasonable expectation of success given the results of Tocque for teaching that the number of hyperproliferative cells is reduced in the presence of a transgene construct comprising the nucleic acid sequence of wild-type p53 and a taxane and Gregory et al for teaching that tumor growth was reduced in nude mice comprising a tumor of H69 cells, when the tumor was injected with A/M/N/53.

Thus, claims 1, 2, 10-13, 15-22, 25-28, 31, 34, 78-80 are obvious.

Claims 1, 2, 10-22, 25-28, 31, 34, 78-80 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Tocque, U.S. Patent 6,262,032, patented July 17, 2001, see IDS, in view of Gregory et al. U.S. Patent 5,932,210, patented August 3, 1999.

As described above in the 103 rejection, claims 1, 2, 10-13, 14-22, 25-28, 31, 34, 38, 78-80 are obvious. However, neither Tocque and Gregory et al. teach an adenoviral vector comprising a partial or total deletion of a protein IX DNA and comprising a nucleic acid sequence encoding a wild-type p53 protein and a deletion of adenovirus early region 4.

While Gregory et al. do not specifically teach that A/C/N/53 or A/M/N/53 have a deletion of early region 4, Gregory et al. teach that this region is non-essential (Gregory, et al., col. 7, lined 49-53) and can be deleted so that insert (i.e. transgene of interest) capacity can be increased (Gregory et al., col. 6, lines 59-62).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made make an A/C/N or A/M/N vector further comprising a deletion of early region 4.

One having ordinary skill in the art would have been motivated to make these vectors in order to obtain a vector with increased insert capacity.

There would have been a reasonable expectation of success given that Gregory et al. teach that early region 4 is non-essential.

Thus, claims 1, 2, 10-22, 25-28, 31, 34, 78-80 are obvious.

Claims 1, 3, 4, 10, 18-22, 25-28, 31, 35, 36, 78-80 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Gjerset, U.S. Patent 6,054,467, patented April 25, 2000.

Gjerset teaches a method of combination therapy, wherein inhibitors of DNA repair mechanisms and p53 gene therapy could be used similarly in conjunction with chemo- or radiotherapeutic intervention (Gjerset, col. 25, under "G. Combination Therapy"). Gjerset teaches that to induce apoptosis in cells, such as malignant cells, an artisan would contact a target cell with an inhibitor of DNA repair and with an expression vector containing wild-type p53, if the cell is p53-negative, and at least one DNA damaging agent (Gjerset, col. 25, 2nd parag. under "G. Combination Therapy"). Gjerset teaches that cancer cells deficient in p53 are sensitized to DNA damaging agents upon expression of exogenous wild-type p53. Gjerset teaches examples of inhibitors of DNA repair (Gjerset, col. 2, lines 43-65), which include non-functional versions of an agent

involved with DNA repair. In the case of DNA-damaging agents, Gjerset teaches that these agents include DNA damaging radiation or chemical compounds that crosslink nucleic acids (e.g. cisplatin), interfere with DNA replication, mitosis, and chromosomal segregation, and agents that disrupt synthesis and fidelity of nucleic acid precursors (Gjerset, col. 2, line 66 to col. 3, line 6 and col., 27, line 20 to col. 28,line 19). Gjerset contemplates that DNA-damaging agents include taxol and taxotere (also known as paclitaxel and docetaxel) (Gjerset, col. 3, line 5). Overall, Gjerset teaches that the goal of the therapy is that p53 gene therapy, in combination with agents that inhibit DNA repair are used trigger apoptosis (Gjerset, col., 5, 2nd parag.).

While Gjerset do not specifically teach an adenoviral vector comprising a nucleic acid sequence encoding wild-type p53, taxol/taxere, and an inhibitor of DNA repair, Gjerset teaches the formula of providing wild-type p53 to a cancer cell deficient in functional p53, administration of a DNA-damaging agent, and an inhibitor of DNA repair. For example, Gjerset teaches in Example III that T47D breast cancer cells were infected with p53 adenovirus treated with SR11220 and/or cisplatin. Gjerset teaches that the treatment with p53 adenovirus, SR11220, and cisplatin reduced T47D cell number more than treatment of p53 adenovirus alone, p53 adenovirus and SR11220, and p53 adenovirus and cisplatin.

Gjerset teaches that adenoviral vectors comprising the nucleic acid sequence encoding p53 can be used and teaches that the advantages for using adenoviral vectors to deliver transgenes include the high infectivity of adenovirus (Gjerset, col. 22, lines 4-12).

Gjerset teaches that the inhibitor of DNA repair, expression vector comprising a nucleic acid encoding wild-type p53, and the DNA damaging agent(s) can be administered at the same time, in a single composition or formulation, or the cancer cell can be contacted with two distinct compositions (Gjerset, col. 25, line 66 to col. 26 line 9). Gjerset teaches that the inhibitor of DNA repair and p53 gene therapy treatment may precede or follow the DNA damaging agent treatment by intervals ranging from minutes to weeks (Gjerset, col. 26, 2nd parag.). Gjerset teaches that administration could include one contacting a cell with both agents within about 12-24 hours of each other and more preferably, within about 6-12 hours of each other, with a delay time of only about 12 hours being most preferred. In some situations it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6, or 7) to several weeks (1, 2, 3, 4, 5, 6, 7, or 8) lapse between the respective administrations (Gjerset, col., 26, 2nd parag.). Gjerset also teaches that more than one administration is contemplated and that various combinations of administration of inhibitor of DNA repair and DNA damaging agent will be used (Gjerset, col. 26, 3rd parag.). For example in column 26, provides a table of possible administration patterns that could be applied. "A" is the inhibitor of DNA repair (and the p53 expression vector) and "B" is the DNA damaging agent. In addition to combinations such as A/A/B, A/B/B, A/B/A, combinations such as, A/A/A/B, B/A/A/A, and A/A/B/A are contemplated. In the case of administration, Gjerset teaches intratumoral administration of an inhibitor of DNA repair, a DNA damaging agent, and/or a gene therapy vector expressing p53 to target cancer cells (Gjerset, col. 3, lines 16-19 and col., 28, 3rd parag.).

It is noted that Gjerset is readable on claims 1 and 4 (and the other dependent claims) as Gjerset teaches an adenoviral vector comprising a nucleic acid sequence encoding wild-type p53 and taxol/taxere. The chemotherapeutic agent of claim 4 is the inhibitor of DNA repair.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to induce apoptosis in a cancer cell comprising administering to a cancer cell deficient in functional p53, an adenoviral vector comprising a nucleic acid sequence encoding wild-type p53, an agent that inhibits DNA repair, and a DNA-damaging agent.

One having ordinary skill in the art would have been motivated to administer an adenoviral vector comprising a nucleic acid sequence encoding wild-type p53, an agent that inhibits DNA repair, and a DNA-damaging agent. Administration of wild-type p53 would sensitize the cell to the chemotherapeutic agents, in a method of inducing apoptosis in cancer cells deficient in wild type p53. Administration of DNA-damaging agents would trigger the DNA repair pathway, which would be dysfunctional, when the cell comprises an inhibitor of the DNA repair pathway. What would ensue would be the apoptotic pathway.

There would have been a reasonable expectation of success given the results of Gjerset teaching that the three components: adenovirus comprising a nucleic acid sequence encoding wild type p53, a DNA-damaging agent, and an inhibitor of DNA repair are more effective at reducing cancer cell number than administering only an adenovirus comprising a sequence encoding wild type p53, or administering an

adenovirus comprising a sequence encoding wild type p53 and a DNA-damaging agent or an inhibitor of DNA repair.

Thus, claims 1, 3, 4, 10, 18-22, 25-28, 31, 35, 36, 78-80 are obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER